IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Curran; *et al.*	:	Art Unit: 1656
	:	
Serial No. 10/078,927	:	Examiner: David J. Steadman
	:	
Filed: February 19, 2002	:	Atty Docket: SJ-01-0032
	:	
For: Cyclin Dependent Kinase 5 Phosphorylation of Disabled 1 Protein	:	

APPEAL BRIEF UNDER 37 CFR § 41.37

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Commissioner for Patents
P.O. Box 1450 Alexandria, VA 22313-1450

Sir:

This appeal Brief is filed pursuant to the "Notice of Appeal to the Board of Patent Appeals and Interferences" filed concurrently herewith.

1. **Real Party in Interest.**

The real party in interest in this application is St. Jude Children's Research Hospital, Inc. by virtue of an assignment executed by both named inventors on February 18, 2002 and recorded in the U.S. Patent Office at Reel/Frame 012919/0525 (4 pages).

2. **Related Appeals and Interferences.**

No other appeals or interferences are known to Appellant, Appellant's legal representative, or assignee St. Jude Children's Research Hospital, Inc. which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

3. **Status of Claims.**

There are a total of 40 claims in this application. Claims 1-3, 9, 12,16-35 and 39-40 have been canceled. Claims 4-8, 10-11, 13-15, and 36-38 are pending and the subject of this appeal.

4. **Status of Amendments.**

No new amendments have been made to the claims.

5. **Summary of Claimed Subject Matter.**

Independent claims 36 and 38

Independent claim 36 is drawn to a method for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample which comprises determining whether the carboxy terminal domain of Disabled 1 protein (Dab1) is phosphorylated on a serine within a candidate sequence, wherein phosphorylation of Dab1 on said serine indicates the presence of active Cdk5 in said sample. Support for claim 36 can be found, at least, at page 3, lines 8 – 13 and lines 21 - 24; page 5, lines 1 – 3; page 7, lines 16 – 29; page 20, lines 8 – 18; page 20, lines 27 – page 21, lines 2; page 21, lines 24 – 31; page 28, lines 11 – 14; and page 29, lines 4 - 8.

Independent claim 38 is drawn to a method for detecting Cdk5 serine kinase activity in a biological sample, which method comprises immunoprecipitation of Dab1 from said biological sample; contacting the immunoprecipitated Dab1 with a phosphoantibody generated using SEQ ID NO:3 as an antigen; detecting binding of the phosphoantibody to a serine within a candidate sequence in the carboxy terminal domain of said Dab1, wherein binding of the phosphoantibody to said serine of said Dab1 in such biological sample indicates the presence of Cdk5 serine kinase activity in said sample. Support for claim 38 can be found, at least, at page 3, lines 8 – 13 and lines 25 – 29; page 9, lines 7 – 9; page 15, lines 16 – 21; page 21, lines 4 – 23; and page 28, lines 14 – 17.

6. **Grounds of Rejection to Be Reviewed on Appeal.**

Issue 1 – Whether claims 4-8 and 36-37 are obvious under 35 U.S.C. 103(a).

Issue 2 – Whether claims 10-11, 13-15 and 38 are obvious under 35 U.S.C. 103(a).

7. **Grouping of Claims.**

Claims 4-8 and 36-37 stand or fall together for the rejection that the claims are obvious. Claims 10-11, 13-15 and 38 stand or fall together for the rejection that the claims are obvious.

8. **Arguments.**

Issue 1 – Whether claims 4 – 8, and 36 - 37 are obvious under 35 U.S.C. 103(a).

The Examiner asserts that claims 4 - 8 and 36 - 37 are obvious based on Curran et al. (US Patent 6,323,177;"Curran") in view of Keshvara et al (J.Biol. Chem. 276:16008 – 16014, 2001; cited as reference AG2 in the IDS filed on 3/25/02; "Keshvara"), Niethammer et al. (Neuron 28:697 – 711, 2000; cited as reference AM1 in the IDS filed on 3/25/02; "Niethammer"), Carr et al. (Analytical Biochem. 239: 180 – 192, 1996; "Carr") and GenBank Accession Numbers 1771281 and 3288851.

The Examiner acknowledges that while the prior art clearly teaches or suggests Dab1 phosphorylation by Cdk5, the combination of references does not appear to explicitly teach or suggest phosphorylation of Dab1 by Cdk5 at residues Ser491 and Ser515. However, the Examiner maintains that one practicing the method as taught or suggested by the combination of prior art, would have practiced a method that is encompassed by the claims.

The purpose of the method is a nonobvious, limiting element of the claimed invention

The purpose of the claimed method, as stated in independent claims 36 and 38, is to detect Cdk5 serine kinase activity in a biological sample. This purpose is accomplished by determining whether a particular candidate sequence within the carboxy terminal domain of Dab1 is serine phosphorylated. The specification teaches that this particular candidate sequence is only phosphorylated by Cdk5. Therefore serine phosphorylation of this candidate sequence is selective for Cdk5 and an indicator of Cdk5 activity.

This discovery of the association between Dab1 serine phosporylation and Cdk5 activity is important. Cdk5 activity in a biological sample cannot be measured directly because Cdk5 must associate with its regulatory subunit, p35, to be activated. Therefore, simply measuring or detecting Cdk5 in a biological sample is not a reliable indicator of whether Cdk5 activity exists. Before the present invention, a simple test to show Cdk5 activity had not been discovered since a substrate that is selectively phosphorylated by Cdk5 had not been identified.

None of the prior art cited by the Examiner teaches or suggests that the candidate sequence within the carboxy terminal domain of Dab1 is selectively serine phosphorylated by Cdk5. Without such a teaching or suggestion, Appellants assert that the claimed method cannot be considered obvious.

The Examiner does not argue that such a teaching or suggestion exists in the prior art. Instead, the Examiner asserts for the first time in the Final Rejection of September 3, 2009 that the prior art need not teach or suggest this association between Dab1 and Cdk5 in order to render the claims obvious because this represents an intended use and does not limit the claimed method. Appellants strenuously disagree.

The purpose of detecting Cdk5 activity appears both in the preamble and the body of independent claims 36 and 38. It is the sole reason taught in the specification for determining whether the candidate sequence within the carboxy terminal domain of Dab1 is serine phosphorylated. Clearly this is a critical feature of the claimed method that is intended to limit its scope.

The Examiner cites MPEP section 2106.II.C to justify ignoring the stated purpose as a limitation of the claimed method, quoting the following portion of this section: "Language that suggests or makes optional but does not require steps to be performed or does not limit a claim to a particular structure does not limit the scope of a claim or claim limitation".

As an initial matter, Appellants point out that this justification is particularly weak. The cited MPEP section merely provides interim guidelines which are acknowledged in the introduction as not constituting substantive rulemaking and which do not have the force and effect of law. Moreover, these are guidelines for determining subject matter eligibility of claims. These are not intended to be guidelines used in an obviousness analysis as the Examiner has done.

Even if these clear facial deficiencies are ignored, Appellants assert that the purpose of their claimed method does not fall within the category of nonlimiting language referred to in this section. The stated purpose is not optional and does require the step of associating Dab1 serine phosphorylation with Cdk5 activity to be performed. Therefore this statement does not justify ignoring the purpose of the claimed method.

To the extent that the Examiner implies that the stated purpose does not limit the claim because it appears in the preamble, Appellants again disagree. While it is possible for a preamble to be nonlimiting, it is clearly limiting in the present case where the preamble is critical to the meaning and vitality of the claim and is used to distinguish the claim from the prior art. *Corning Glass Works,* 868 F.2d at 1257, 9 USPQ2d at 1966 (Fed.Cir.1989); *Bell Communications Corp.*, 34 USPQ2d 1816 (Fed. Cir 1995); *Catalina Marketing Int'l, Inc. v. Coolsavings.com, Inc.*, 01-1324 (Fed. Cir. May 8, 2002); *In re Cruciferous Sprout Litig.*, 301 F.3d 1343, 1346-48, 64 USPQ2d 1202, 1204-05 (Fed. Cir. 2002), *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1333-34, 68 USPQ2d 1154, 1158 (Fed. Cir. 2003); *Metabolite Labs., Inc. v. Corp. of Am. Holdings*, 370 F.3d 1354, 1358-62, 71 USPQ2d 1081, 1084-87 (Fed. Cir. 2004); *See also* Section 2111.02 II. of the MPEP. In addition Appellants note that the stated purpose appears not only in the preamble of independent claims 36 and 38 but it also appears in the body of these claims.

No motivation to combine references

Furthermore, Appellants assert the present invention is not obvious because there was no motivation to combine the cited references in the manner suggested by the Examiner to arrive at the claimed method. Given the prior art, the Examiner asserts it would have been obvious to one of skill in the art to combine the teaching of Curran, Niethammer, Keshvara and GenBank Accession Numbers 1771281 and 3288851 to immunoprecipitate Dab1 from mouse brain extract with and without catalytically active Cdk5, to determine whether or not serines at positions 260, 400, 481, 491, and 515 are phosphorylated, and to determine the serine(s) that are phosphorylated by Cdk5 in accordance with the methodology of Niethammer and Keshvara.

Alternatively, the Examiner asserts that it would have been obvious to combine Curran, Keshvara and Carr to immunoprecipitate Dab1 from mouse brain extract with catalytically active Cdk5 to determine its potential sites of phosphorylation according to the method of Carr. That by doing this, one would have practiced the active method steps as recited in the claims. One would have been motivated to do this because of the teachings of Curran that Cdk5 phosphorylates serines of Dab1, the sites of Cdk5 phosphorylation of Dab1 can be identified, and may have

"significant relevance" to screen for agonists and antagonists because Cdk5 has been implicated as a kinase associated with increased phosphorylation of neurofibrillary tangles in AD. According to the Examiner, one would have had a reasonable expectation of success for mutating Dab1 serines at positions 260, 400, 481, 491 and 515 to alanine, individually and combinatorially, and determining the serine(s) that are phosphorylated by Cdk5 using the methodology of Niethammer and Keshvara because of the results of Curran, Niethammer, Keshvara and GenBank Accession Nos. 1771281 and 3288851.

Appellants disagree. The present invention is based on the discovery that Dab1 is selectively phosphorylated by Cdk5 on serines 491 and 515 *in vivo*. Although Curran teaches that Dab1 is phosphorylated by Cdk5 activity *in vitro*, there is no suggestion in this reference or other prior art references that Cdk5 selectively phosphorylates Dab1 in a biological (*in vivo*) sample, nor do they teach which serines might be selectively phosphorylated by Cdk5. Curran only suggests screening for inhibitors and agonists of *in vitro* phosphorylation of Dab1 in connection with reelin binding to very low density lipoprotein receptor (VLDLR). Keshvara teaches *in vitro* and *in vivo* methods for identifying Dab1 phosphorylation by Src. Niethammer suggests serines 491 and 515 as potential sites for cdk (not just Cdk5) activity. Niethammer does not provide substrate sites that indicate specific Cdk5 activity. Since there is nothing in Keshvara, Curran or Niethammer to suggest Dab1 is selectively phosphorylated by Cdk5 in a biological sample, there is no motivation for one to visually inspect the Dab1 amino acid sequences of Gen Bank Accession Number 1771281 and 3288851 and identify serines 491 or 515 as serines that are phosphorylated selectively by Cdk5.

Until Appellants showed in the present invention, for example by the experiments described in the specification on pages 19 – 22 that Dab1 is an *in vivo* target of Cdk5, one could not have known or predicted that certain sites in Dab1 would be phosphorylated only by Cdk5 and provide a method for detecting Cdk5 activity. While it was known that Cdk5 phosphorylates Dab1 *in vitro*, Appellants conducted experiments to localize and identify the particular sites on Dab1 that could be phosphorylated *in vivo* by Cdk5, (page 19, line 20 – page 21, line 2), generated Dab1 tryptic peptides used in the production of a phosphopeptide-specific antibody

(page 21, lines 3 – 23), and showed that Dab1 is specifically phosphorylated by Cdk5 (page 21, line 24 – page 22, line 25).

For the reasons set forth above, Appellants submit (1) the purpose of the claimed method is critical to the meaning of the claim and limits the claimed method, and (2) since the prior art cited by the Examiner fails to teach or suggest the ability to detect Cdk5 activity by determining whether a candidate sequence within the carboxy terminal domain of Dab1 is serine phosphorylated, there is no motivation to combine the prior art references. Therefore, the prior art fails to render claims 4-8 and 36-37 obvious.

Issue 2 – Whether claims 10-11, 13-15 and 38 are obvious under 35 U.S.C. 103(a).

The Examiner rejected claims 10-11, 13-15 and 38 under 35 U.S.C. 103(a) as being unpatentable over Curran in view of Keshvara, Niethammer, Carr and GenBank Accession Numbers 1771281 and 3288841 as applied to claims 4 – 8 and 36 - 37 above and further in view of Howell et al.(Genes Develop. 13:633 – 648, 1999; cited as reference AY1 in the IDS filed on 3/25/02; "Howell") , Fu et al. (Nature Neurosci. 4:374-381; "Fu"), Michalewski et al. (Analytical Biochem. 276: 254 – 257, 1999; "Michalewski"), and Zhen et al. (J. Neurosci. 21:9160 – 9167, 2001: "Zhen"). These claims limit the claimed methods to detection of Dab1 phosphorylation using an antibody that binds to Dab1 only when it is phosphorylated on serine or to an antibody generated against SEQ ID NO:3.

This rejection suffers from the same deficiencies as the first rejection

Applicants' arguments stated above show that it was not obvious that Cdk5 serine kinase activity could be determined by determining whether the carboxy terminal domain of Dab1 was phosphorylated on a serine within a candidate sequence. Nothing in the prior art suggests that the serines within a candidate sequence of Dab1, serines 491 and 515, are only phosphorylated by Cdk5. For the reasons stated above, there is nothing in the prior art references of Curran, Keshvara, Niethammer, Carr and the recited GenBank Accession Numbers to suggest the inventions in claims 4-8 and 36-37. Thus combining Howell, Fu, Michalewski and Zhen with

Curran, Keshvara, Niethammer, Carr and the recited GenBank numbers does not render the antibodies of claims 10 - 11, 13 -15 and 38 obvious. Therefore the rejection should be reversed.

9. **Claims Appendix.**

10. **Evidence Appendix.**

None (see Evidence Appendix)

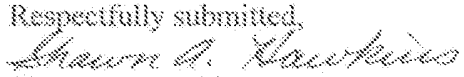
11. **Related Proceeding Appendix.**

None (see Related Proceeding Appendix)

Conclusion.

For the foregoing reasons, Appellants believe that the Examiner's rejections of Claims 4-8, 10-11, 13-15, and 36-38 are erroneous and should be reversed.

Respectfully submitted,



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Claims Appendix

4. The method of claim 36 wherein said biological sample is isolated from an organism selected from the group consisting of mouse and human.

5. The method of claim 36 wherein said biological sample is isolated from the group consisting of brain and blood.

6. The method of claim 36 wherein said biological sample is isolated from a cell culture.

7. The method of claim 36 wherein said Dab1 phosphorylation occurs *in vivo*.

8. The method of claim 36 which comprises immunoprecipitating said Dab1 from said biological sample prior to said determining step using an antibody that binds to Dab1 phosphorylated and unphosphorylated on said serine.

10. The method of claim 36 wherein Dab1 phosphorylation is determined using an antibody that binds to Dab1 only when it is phosphorylated on said serine.

11. The method of claim 10 wherein said antibody is raised against SEQ ID NO:3.

13. The method of claim 10 wherein said antibody is polyclonal.

14. The method of claim 10 wherein said antibody is monoclonal.

15. The method of claim 10 wherein Dab1 phosphorylation is determined by using techniques consisting of radioimmunoassay, ELISA, "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitation reactions, immunodiffusion assays, in situ immunoassays, western blots, precipitation reactions, agglutination assays, complement fixation assays, immunofluorescence assays, protein A assays, immunoelectrophoresis assays, mass spectrometry and antibody array.

36. A method for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample, which method comprises determining whether the carboxy terminal domain of Disabled 1 protein (Dab1) in said sample is phosphorylated on a serine within a candidate sequence, wherein phosphorylation of Dab1 on said serine indicates the presence of active Cdk5 in said sample.

37. The method of claim 36 wherein said serine is selected from the group consisting of a serine corresponding to position 3 of SEQ ID NO:1, such position being determined by alignment of Dab1 with SEQ ID NO:1 and a serine at position 21 of SEQ ID NO:2, such position being determined by alignment of Dab1 with SEQ ID NO:2.

38. A method for detecting cyclin dependent kinase 5 (Cdk5) serine kinase activity in a biological sample, which method comprises immunoprecipitation of Dab1 from said biological sample; contacting the immunoprecipitated Dab1 with a phosphoantibody generated using SEQ ID NO:3 as an antigen; detecting binding of the phosphoantibody to a serine within a candidate sequence in the carboxy terminal domain of said Dab1, wherein binding of the phosphoantibody to said serine of said Dab1 in such biological sample indicates the presence of Cdk5 serine kinase activity in said sample.

Evidence Appendix

None

Related Proceedings Appendix

None